

Ventilation and Hæmodynamics in Heart Disease

NIKOS GAZETOPOULOS, HYWEL DAVIES*, CHARLES OLIVER, AND
DENNIS DEUCHAR

From the Cardiac Department, Guy's Hospital, London S.E.1

The ventilatory response to exercise in patients with heart disease is intimately related to the dyspnoea which they suffer, and a better knowledge of the factors concerned in the genesis of hyperventilation would be of value in understanding the cause of their symptoms. The work reported here is concerned with a study of these factors.

The control of ventilation has for long been studied intensively in the domain of physiology both in animals and healthy human subjects. Increasingly in recent years reports have been published describing studies in patients, usually with mitral valve disease and left heart failure, and dealing with the striking effort hyperventilation that is often seen in these conditions. In such patients several features have been considered as responsible for this.

Usually the cardiac output is low and does not increase normally with effort; tissue hypoxia occurs, the oxygen debt increases, and the oxygen saturation of venous blood becomes abnormally low (Harrison and Pilcher, 1930; Katz *et al.*, 1934; Donald, Bishop, and Wade, 1954). Several reports suggest that there is a greater production of lactate in these patients compared with normal subjects at the same exercise level (Meakins and Long, 1927; Huckabee and Judson, 1958; Donald *et al.*, 1961). Neither the limitation of cardiac output nor the increased lactate production, however, appears to be adequate to explain the hyperventilation seen (Donald *et al.*, 1954; Cotes, 1955; Harris, Bateman, and Gloster, 1962).

Abnormal lung function (Frank *et al.*, 1953; Carroll, Cohn, and Riley, 1953; Riley *et al.*, 1956; Raine and Bishop, 1963) and abnormal blood gases (Blount, McCord, and Anderson, 1952; West *et al.*, 1953) have been observed in some patients with heart disease, but no direct relation has been

found between these and the observed degree of hyperventilation on effort (Cotes, 1955; Donald, 1959).

Reflexes from the pulmonary artery (Nonidez, 1936; Krael, 1960), pulmonary veins (Korn *et al.*, 1960), or pulmonary parenchyma (Widdicombe, 1954) may be implicated in the sensations accompanying effort hyperventilation. While such reflexes have been found in animals (Aviado and Schmidt, 1955; Costantin, 1959; Widdicombe, 1961), in man their significance is uncertain and questionable (Dawes and Comroe, 1954; Downing, 1957; Widdicombe, 1961).

This paper deals with the relation between the hæmodynamic changes and the ventilation on effort observed during cardiac catheterization. While hyperventilation often occurs under these circumstances, dyspnoea is less common since the exercise load is usually insufficient to bring this about. Study of the relation between metabolic changes and ventilation, both during cardiac catheterization and at higher exercise levels is reported in a subsequent paper (Gazetopoulos, Davies, and Deuchar, 1966). Dyspnoea was usually present in the latter circumstances and the relevant observations are described in another paper.

SUBJECTS AND METHODS

The study is based on observations made in 144 patients with heart disease and in 12 normal subjects, the latter having been investigated in most cases to prove the innocence of a murmur. Of these 156 subjects, 70 have been investigated by us, and the data for the others have been obtained from the records of our laboratory, the technique of study having been standard throughout. The criteria for selection of the subject have been based entirely on the adequacy of the hæmodynamic and spirometric records and the sound establishment of the diagnosis, usually by operation. Patients with intracardiac shunts were not included in this study.

In an attempt to separate the various factors which

Received March 12, 1965.

* Supported by a U.S. Public Health Service Fellowship (5-F2-HE-19, 427-02) from the National Heart Institute.

TABLE I

Group	Subjects	No.
I	Normals	12
II	{ Aortic stenosis	19
III	{ Cardiomyopathy	4
IV	Mitral valve disease	85
V	Pulmonary hypertension	9
	Isolated pulmonary stenosis	27

may influence the ventilation, we have divided the patients into different groups (Table I).

All the subjects were lightly sedated before study; the sedation used was varied to suit individual patients but was usually either a small dose of papaveretum or a barbiturate. Right heart catheterization was performed in the usual manner, an indwelling needle was placed in the brachial artery, and spirometry was performed with simultaneous blood sampling for Fick output determination. After this, the catheter was advanced to a pulmonary wedge position and leg exercise performed using a spring or bicycle ergometer. Special attention was paid to the maintenance of a constant exercise level. Simultaneous brachial arterial and pulmonary capillary (wedge) pressures were recorded continuously. Between the third and fourth minute of exercise the wedged

catheter was withdrawn into the main pulmonary artery, and the pulmonary arterial pressure was recorded. After five minutes of exercise, spirometry was performed and two brachial and two pulmonary arterial samples were taken. The mean of each pair of these readings was used for the calculation of the cardiac output during exercise by the Fick principle. In cases of aortic stenosis this procedure was followed by left heart catheterization. Some modification of the technique was used for patients with pulmonary stenosis. The catheter was placed in the pulmonary artery, exercise was begun, and after sampling and spirometry it was withdrawn into the right ventricle and atrium for pressure recordings.

Exercise spirometry was continued for 3 minutes: the closed circuit method described by Donald and Christie (1949) was used, as this permits the use of room air as opposed to oxygen. The total duration of exercise was 10 to 15 minutes. Oxygen uptake was corrected to STPD, the ventilatory rate and volume were measured from the spirometric tracings, the latter being corrected to BTPS. We have used the oxygen uptake uncorrected for body surface areas as an index of work level (Wahlund, 1948; Astrand, 1952), and have, therefore, corrected neither the ventilation nor the cardiac output for body surface area.

TABLE
MEAN VALUE AND STANDARD ERROR OF MEAN OF PHYSIOLOGICAL AND

Group	Age (yr.)	BSA (m. ²)	O ₂ capacity (vol. %)	$\dot{V}O_2$ (l./min.)	CO (l./min.)	Heart rate	\dot{V} (l./min.)	Resp. rate	VE	Sao ₂
I (12)	27.9 ± 3.5	1.72 ± 0.1	18.78 ± 0.7	Rest 222.2 ± 15.6 Ex. 600.0 ± 60.4	6.42 ± 0.5 9.69 ± 0.8	79.2 ± 3.1 112.8 ± 4.4	6.9 ± 0.6 14.8 ± 1.4	15.2 ± 1.3 18.7 ± 1.5	3.25 ± 0.3 2.54 ± 0.2	97.7 ± 0.5 97.6 (9) ± 0.6
II (23)	39.67 ± 3.3	1.71 ± 0.03	18.98 ± 0.45	Rest 229.3 ± 8.8 Ex. 434.8 ± 28.3	4.83 ± 0.3 6.53 ± 0.5	75.8 ± 3.7 96.4 ± 3.3	7.2 ± 0.4 13.6 ± 1.1	12.4 ± 0.5 18.4 ± 1.1	3.13 ± 0.1 3.23 ± 0.2	95.5 ± 0.5 95.1 (12) ± 0.8
III (85)	38.29 ± 1.0	1.63 ± 0.02	18.38 ± 0.27	Rest 207.4 ± 4.4 Ex. 392.4 ± 10.0	3.58 ± 0.1 4.75 ± 0.2	78.8 ± 1.8 107.3 ± 2.8	7.28 ± 0.2 15.06 ± 0.5	15.2 ± 0.5 23.4 ± 0.7	3.58 ± 0.1 3.91 ± 0.1	94.9 (83) ± 0.3 95.47 (33) ± 0.4
IV (9)	37.56 ± 4.8	1.62 ± 0.06	19.94 ± 0.66	Rest 210.8 ± 13.7 Ex. 466.8 ± 33.8	4.42 ± 0.70 5.63 ± 0.5	78.4 ± 6.3 102.0 ± 7.2	6.97 ± 0.6 15.4 ± 2.2	17.8 ± 1.5 24.2 ± 1.4	3.48 ± 0.5 3.29 ± 0.4	90.4 ± 1.9 90.4 ± 2.2
V (27)	23.2 ± 2.4	1.59 ± 0.05	18.62 ± 0.3	Rest 227.9 ± 10.8 Ex. 516.0 ± 32.6	5.1 ± 0.3 7.1 ± 0.4	72.9 ± 2.5 103.4 ± 3.1	5.62 ± 0.2 14.8 ± 0.9	15.0 ± 0.7 21.9 ± 1.1	2.53 ± 0.1 2.9 ± 0.1	97.3 ± 0.4 96.7 ± 0.4

Note: Number of cases in whom measurements were made is given in brackets beneath the group number in the first column and apply throughout except where given separately in brackets.

BSA, body surface area; O₂ capacity, oxygen capacity at rest; $\dot{V}O_2$, oxygen consumption at standard temperature (0° C.), pressure (760

The heart rate was obtained from the electrocardiogram and pressure records. Pressures were recorded with inductance manometers, the mid-axillary line being used as a basis of reference. The pulmonary vascular resistance was calculated in the usual manner (Wood, 1954).

RESULTS

These are shown in Table II, where the mean values, and the standard errors of the means for each group and parameter, are given: they will be discussed separately for each diagnostic group.

It will be observed that the exercise level, as judged by the oxygen uptake, varies from group to group: this is a consequence of the lack of volition or ability on the part of the more disabled patients to undertake any more than the lower levels of exercise. In view of this, the groups cannot be compared without reference to the oxygen uptake, and in an attempt to overcome this difficulty we have made use of the ventilatory equivalent (VE, ventilation in litres per min. BTPS per 100 ml. oxygen consumption STPD). This is, as discussed

below, a rough index only and we have therefore also assessed the deviation of the ventilation from the anticipated mean normal for that exercise level.

Group I: Normal Subjects (12). Our results (Table II) are generally in agreement with those of other authors (Riley *et al.*, 1948; Hickam and Cargill, 1948; Dexter *et al.*, 1951; Lewis *et al.*, 1952; Slonim *et al.*, 1954; Donald *et al.*, 1955; Freedman *et al.*, 1955; Barratt-Boyes and Wood, 1957).

In Fig. 1 and 2, oxygen uptake is compared with ventilation on the one hand and cardiac output on the other during supine exercise at cardiac catheterization. In both figures the open symbols refer to our patients, and the closed symbols to data taken from the published material as indicated. Where necessary, the figures taken from other authors have been adjusted, using their data standardized for temperature and pressure, to yield absolute values, rather than values related to body surface area. The lines given in Fig. 1 represent the upper and lower limits of normal found by Davies, Gazetopoulos, and Oliver (1965) in a study of 10 normal

II

HAEMODYNAMIC DATA AT REST AND ON EXERCISE IN 5 GROUPS OF PATIENTS STUDIED

SvO ₂	PCV mean	Pressures (mm. Hg)						PVR units	
		Pulmonary arterial			Systemic				
		Syst.	Diast.	Mean	Syst.	Diast.	Mean		
78.4 ± 2.1	9.0 (11) ± 0.9	23.9 ± 1.3	9.3 ± 0.5	14.9 ± 0.9	111.3 (10) ± 5.8	63.4 (10) ± 4.5	78.7 (7) ± 6.1	1.07 (11) ± 0.17	
63.8 ± 3.0	10.0 (7) ± 0.8	27.8 (10) ± 1.3	11.3 (10) ± 0.9	17.5 (8) ± 1.8	127.0 (8) ± 9.8	73.2 (8) ± 7.0	86.7 (6) ± 9.3	0.79 (7) ± 0.21	
69.0 ± 1.7	14.0 ± 1.4	37.1 ± 3.5	18.2 ± 2.2	24.9 ± 2.5	110.3 (20) ± 4.7	64.8 (20) ± 2.6	87.3 (11) ± 4.7	2.59 ± 0.47	
58.1 ± 2.5	21.0 (21) ± 2.1	50.6 ± 5.3	24.2 ± 2.6	35.4 (21) ± 4.2	128.6 (12) ± 7.4	69.6 (12) ± 3.7	94.6 (9) ± 3.7	2.90 (21) ± 0.80	
62.4 ± 1.0	19.0 ± 0.9	51.6 ± 2.9	25.4 ± 1.5	34.8 ± 2.0	120.5 (60) ± 3.3	71.8 (59) ± 2.2	85.9 (17) ± 5.1	4.90 ± 0.60	
47.1 ± 1.4	30.0 (82) ± 1.0	76.9 ± 4.1	39.3 ± 2.1	53.6 ± 2.9	139.2 (33) ± 5.1	80.1 (33) ± 3.2	98.6 (17) ± 6.1	6.4 (82) ± 0.8	
64.0 ± 3.2	7.9 (8) ± 1.1	73.7 ± 9.5	29.8 ± 4.4	46.4 ± 5.5	129.4 ± 6.2	75.0 ± 4.9	90.0 (6) ± 10.2	10.8 (8) ± 2.7	
47.3 ± 4.3	10.9 (7) ± 1.7	98.0 ± 11.1	43.8 ± 5.1	62.9 ± 6.2	143.8 (6) ± 9.1	84.2 (6) ± 9.8	100.0 (6) ± 9.8	10.2 (7) ± 2.8	
								RV	
								Sys.	Diast.
72.3 ± 1.0	—	20.6 (25) ± 1.0	9.8 (25) ± 0.6	14.5 (24) ± 0.7	118.1 (24) ± 2.7	69.2 (24) ± 1.5	84.5 (22) ± 2.0	72.8 (26) ± 7.6	9.6 (26) ± 0.9
56.9 ± 1.6	—	28.2 (21) ± 1.5	11.8 (21) ± 0.8	18.6 (19) ± 0.9	137.6 (22) ± 3.8	77.8 (22) ± 2.2	97.8 (17) ± 3.3	98.0 (25) ± 8.8	11.4 (25) ± 1.2

mm. Hg), dry; CO, cardiac output; \dot{V} , ventilation at body temperature, pressure saturated with water vapour; VE, ventilatory equivalent; Sao₂, arterial oxygen saturation; SvO₂, mixed venous oxygen saturation; PCV, pulmonary capillary venous (wedge), PVR, pulmonary vascular resistance; RV, right ventricle.

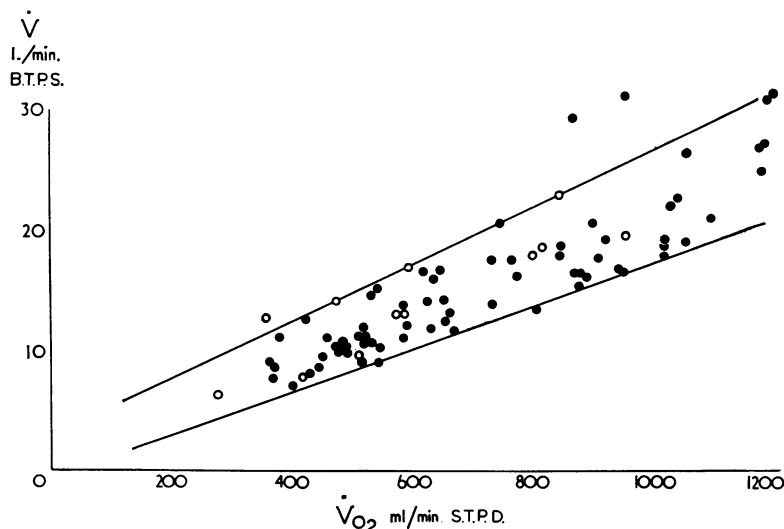


FIG. 1.—Ventilation and oxygen uptake in normal subjects during cardiac catheterization. This figure gives the relation between ventilation and oxygen uptake obtained from exercising normal subjects during cardiac catheterization. The solid circles represent data obtained from the following authors: Barratt-Boyes and Wood (1957); Dexter *et al.* (1951); Donald *et al.* (1955); Freedman *et al.* (1955); Hickam and Cargill (1948); Lewis *et al.* (1952); Riley *et al.* (1948). The open circles are our data. The heavy lines show the upper and lower limits of normal obtained from another study (Davies *et al.*, 1965).

subjects exercised in the upright position on a bicycle ergometer. It is apparent that there is no significant difference between these 2 sets of data. The lines given in Fig. 2 again represent the upper and lower limits of normal. These lines will therefore be used in later figures.

The normal range of the VE given in published

reports is 2.2 to 2.6 (Gray, 1950; Grodins, 1950). It is apparent from Fig. 1 that particularly at the lower exercise levels both the range and the upper limit are greater than this; the latter is 3.0 at an oxygen uptake of 500 ml./min. and 3.5 at 300 ml./min. Most of the results presented in this paper refer to patients exercising with an oxygen uptake

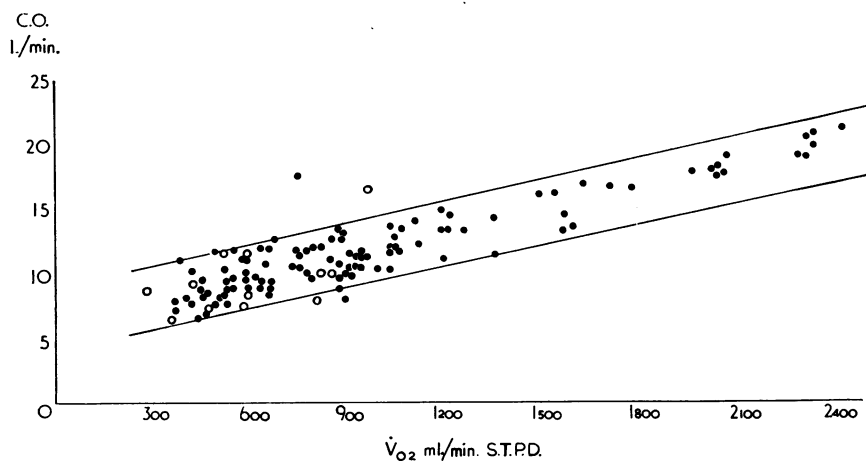


FIG. 2.—Cardiac output and oxygen uptake in normal subjects during supine exercise. The closed circles represent data obtained during catheterization of normal subjects by the following authors: Dexter *et al.* (1951); Donald *et al.* (1955); Freedman *et al.* (1955); Lewis *et al.* (1952); Slonim *et al.* (1954). Our data are represented by the open circles. The heavy lines show the upper and lower limits of normal.

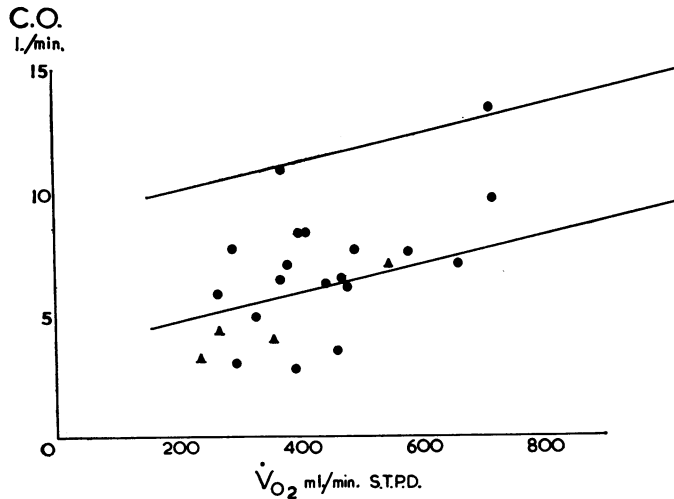


FIG. 3.—Cardiac output and oxygen uptake in patients with aortic stenosis (circles) and cardiomyopathy (triangles). The heavy lines represent the limits of normal shown in Fig. 2.

of about 400 ml./min., corresponding to an upper level of 3.2 for the VE. Cunningham (1963) has also found that at these lower exercise levels the upper limit of normal VE is higher than that usually given.

Group II: Aortic Stenosis (19) and Cardiomyopathy (4). Both conditions are presented together since they share the common feature of abnormal function of the left ventricle. Fig. 3 shows the relation between cardiac output and oxygen uptake on exercise: circles referring to aortic stenosis and triangles to cardiomyopathy. As anticipated the

cardiac output in a number of cases is below the normal range.

Figure 4 shows the exercise ventilation in relation to the oxygen uptake. The patients with impaired cardiac output (i.e. those who fall below the lower limit of normal as shown in Fig. 3) are now represented by solid symbols. It is seen that these low-output cases have a ventilatory response above the upper limit of normal, whilst most of the patients with normal cardiac output show a normal ventilatory response. Only in two patients with normal cardiac output is the ventilation significantly in

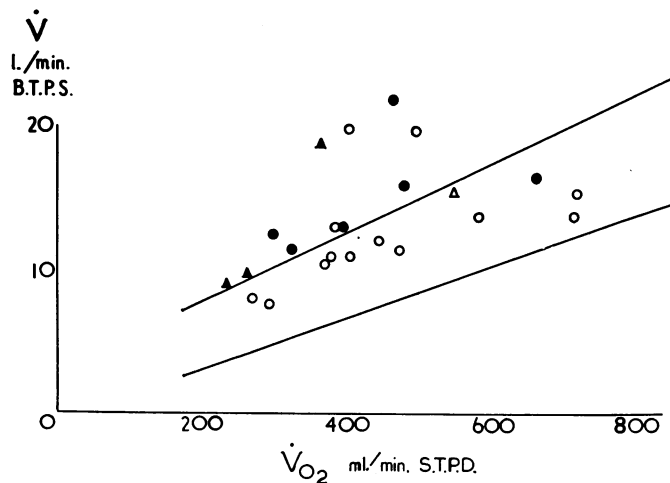


FIG. 4.—Ventilation and oxygen uptake in patients with aortic stenosis (circles) and cardiomyopathy (triangles). The open symbols represent patients with a normal response of cardiac output to exercise, and the closed symbols those with cardiac output below the limits of normal shown in Fig. 3. The heavy lines give the limits of normal as in Fig. 1.

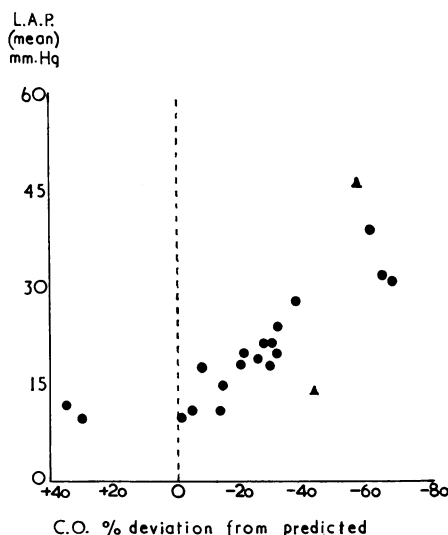


FIG. 5.—Left atrial indirect pressure and percentage deviation of cardiac output from normal (see text) in patients with aortic stenosis or cardiomyopathy during supine catheter exercise. Symbols as in Fig. 3. There is a highly significant correlation between those two variables ($r=0.8$, $p<0.001$).

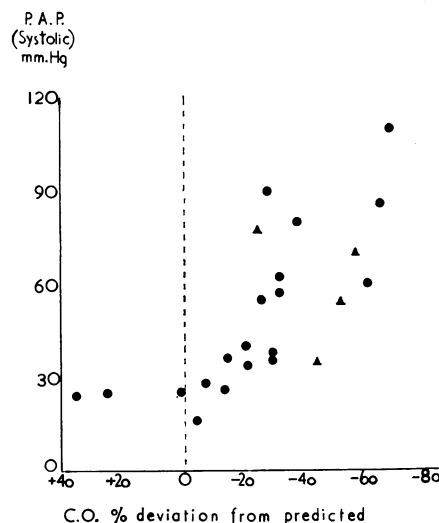


FIG. 6.—Pulmonary artery systolic pressure and percentage deviation of cardiac output from normal (see text) in patients with aortic stenosis or cardiomyopathy during supine catheter exercise. Symbols as in Fig. 3. Again, a highly significant correlation is noted between these two variables ($r=0.7$, $p<0.001$).

excess of normal; none of the observed haemodynamic features of these cases, such as LV pressure, BA pressure, transvalvar gradient, etc. distinguishes them from the remaining members of the group.

At first sight it seems that effort hyperventilation in this group was related to impaired cardiac output. On examining the relation between the impairment of cardiac output and the indirect left atrial pressure on exercise, however, it is seen that there is a good

positive correlation between them (Fig. 5). A similar relation exists between the impairment of cardiac output and the pulmonary arterial pressure on exercise (Fig. 6). In both figures the predicted cardiac output has been taken as the mean value for the corresponding oxygen uptake in normal subjects (Fig. 2), deduced as described above.

Any or all of these three factors—low output, high left atrial pressure, or high pulmonary arterial

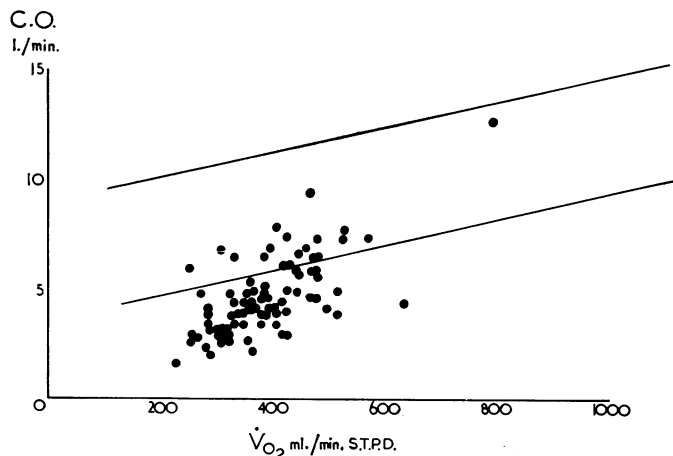


FIG. 7.—Cardiac output and oxygen uptake during supine catheter exercise in patients with mitral stenosis. The heavy lines represent limits of normal as in Fig. 2.

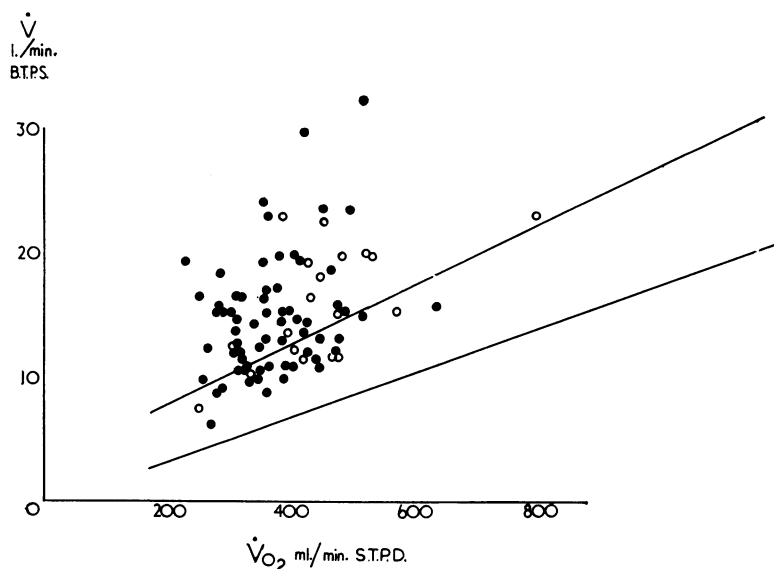


FIG. 8.—Ventilation and oxygen uptake during supine catheter exercise in patients with mitral stenosis. Open circles represent patients with a normal response of cardiac output to exercise, and closed circles those with a cardiac output below normal (see Fig. 7). Although many subjects have raised ventilation, those with a low cardiac output do not behave differently from those with a normal cardiac output.

pressure—could, therefore, be responsible for the hyperventilation observed. The following groups help to clarify the issue.

Group III: Mitral Valve Disease (85). The haemodynamic changes are similar to those reported by many authors (Gorlin *et al.*, 1951; Ferrer *et al.*, 1952; Donald *et al.*, 1954).

Figure 7 shows the relation between cardiac output and oxygen consumption on exercise: the

expected limitation of the former is well shown. Fig. 8 illustrates the relation between ventilation and oxygen consumption. Cases with normal cardiac output are shown by open circles and those with low output by closed circles. It is apparent that hyperventilation is a common finding, but that the cardiac output is not a dominant determinant in that many cases with normal output lie well above the upper limit of normal ventilation and vice versa.

V.E.

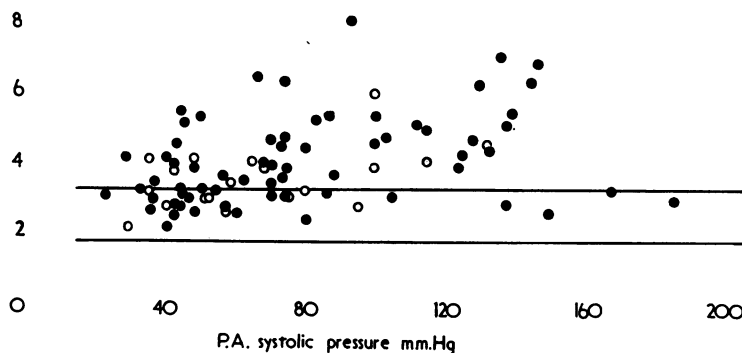


FIG. 9.—Ventilatory equivalent and pulmonary artery systolic pressure in patients with mitral stenosis. Symbols as in Fig. 8. The heavy lines represent the normal range of the ventilatory equivalent for an oxygen uptake of 400 ml./min. Note that several of the subjects with the highest pulmonary artery systolic pressure on exercise have a normal ventilatory equivalent.

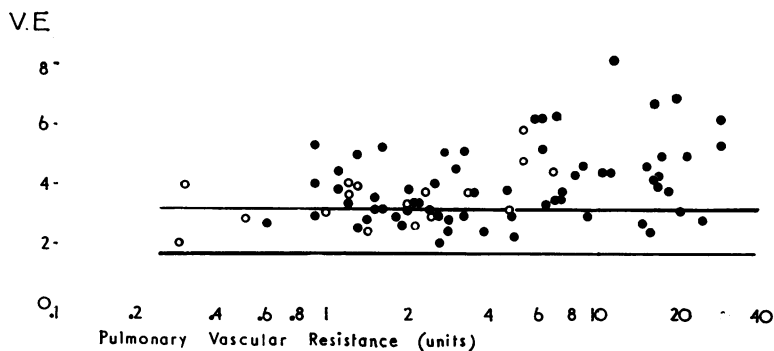


FIG. 10.—Ventilatory equivalent and pulmonary vascular resistance in patients with mitral stenosis. Symbols as in Fig. 8. Although with higher values of pulmonary vascular resistance a greater number of patients have a raised ventilatory equivalent, many fall within the normal range.

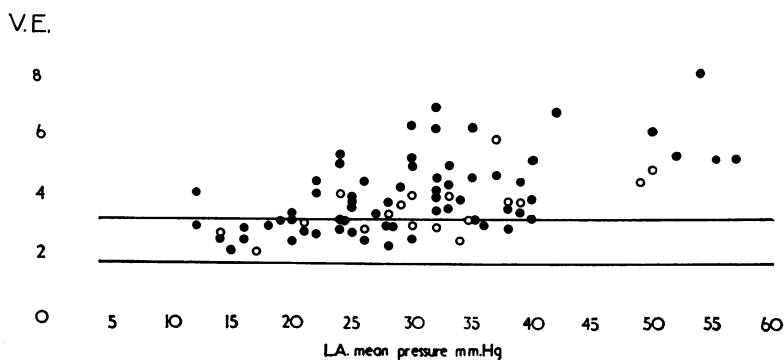


FIG. 11.—Ventilatory equivalent and indirect left atrial pressure in patients with mitral stenosis. Symbols as in Fig. 8. There is a suggestion that the ventilatory equivalent increases with an increase in left atrial pressure, but the relationship is not striking.

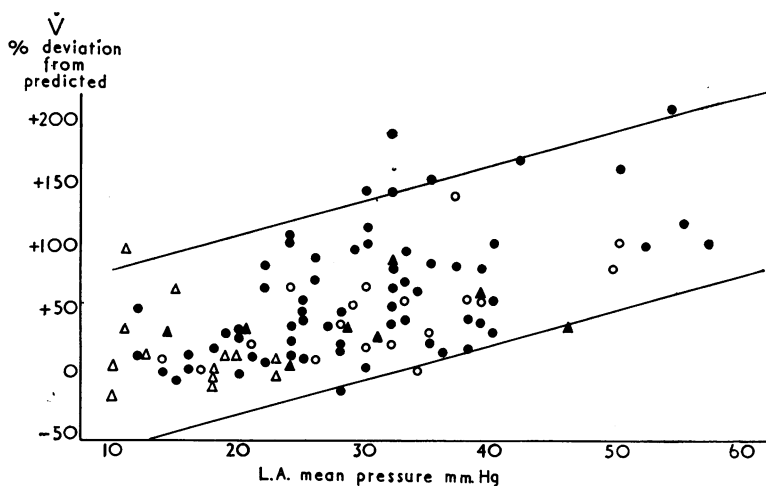


FIG. 12.—Percentage deviation of ventilation from predicted (see text) and indirect left atrial pressure in patients with mitral stenosis (circles), aortic stenosis, and cardiomyopathy (triangles). Open symbols represent patients with normal cardiac output and closed symbols those with a lowered cardiac output on effort. The heavy lines represent the 95 per cent confidence limits of the data obtained with patients with mitral stenosis. A highly significant relationship exists between these two variables ($r=0.6$, $p<0.001$).

TABLE III
PRE- AND POST-OPERATIVE FINDINGS IN PATIENTS STUDIED AT REST AND ON EFFORT

Case No., sex, and age	BSA (m. ²)	Resting O ₂ cap. (vol. %)	V̇O ₂ (ml./min.)		Heart Rate		CO (l./min.)		V̇ (l./min.)		Resp. rate		VE		PCV mean pressure (mm. Hg)		PA pressure (mm. Hg) S/D/Mean	
			Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.	Rest	Ex.
1 F 32	1.4	Pre-op. 16.0 Post-op. 18.9 (26 mth.)	162 208	383 405	70 86	132 162	2.4 3.1	3.5 3.1	6.6 5.2	17.2 14.5	15 12	26 22	4.1 2.5	4.5 3.6	26 19	39 31	65/33/49 37/21/27	105/50/75 70/43/53
2 F 26	1.6	Pre-op. 17.8 Post-op. 17.9 (15 mth.)	250 232	520 466	85 72	150 84	3.0 4.3	4.0 6.1	9.0 8.8	20.6 11.5	15 10	22 15	3.7 3.8	4.0 2.5	25 18	— 26	83/63/57 42/20/31	98/68/82 60/27/43
3 F 31	1.5	Pre-op. 19.7 Post-op. 18.3 (23 mth.)	186 206	316 396	70 60	120 75	2.7 3.7	2.8 5.1	6.6 5.5	12.6 9.3	15 14	23 19	3.5 2.7	4.0 2.4	19 10	32 16	81/46/58 50/20/30	115/58/78 84/36/51
4 F 35	1.7	Pre-op. 17.0 Post-op. 18.0 (36 mth.)	233 237	460 400	60 70	85 92	3.8 5.6	5.9 5.5	8.6 6.4	17.0 13.2	13 13	26 20	3.7 2.7	3.7 3.3	25 8	30 19	50/25/35 25/10/18	90/55/70 40/20/30
5 F 40	1.5	Pre-op. 20.6 Post-op. 20.9 (12 mth.)	200 200	315 396	— 60	— 85	2.3 2.6	2.3 3.5	7.7 6.6	16.5 13.7	14 15	27 25	3.8 3.3	5.2 3.4	32 11	38 28	—/92 24/13/23	—/120 65/30/49
6 F 36	1.7	Pre-op. 18.0 Post-op. 18.5 (14 mth.)	192 184	270 237	108 90	150 120	2.6 2.9	2.2 2.7	8.8 6.9	24.2 10.0	16 14	20 14	4.6 3.7	9.0 4.2	24 16	— 22	64/46/53 40/20/28	110/73/96 75/50/60
7 M 29	1.8	Pre-op. 13.8 Post-op. 17.0 (14 mth.)	350 258	530 525	— 74	— 92	3.9 4.9	7.8 7.4	8.8 8.5	19.6 20.0	8 13	21 26	2.5 3.3	3.7 3.8	20 17	— 38	47/33/40 34/20/28	92/72/63 68/48/55
8 F 27	1.4	Pre-op. 16.0 Post-op. 14.7 (30 mth.)	220 168	352 276	80 88	115 114	3.4 2.7	4.0 2.9	8.8 6.6	18.5 16.5	20 12	28 30	4.0 3.9	5.2 6.0	20 16	56 22	48/29/40 40/18/26	115/63/85 50/24/33

Note: The interval between operation and the second study is given in months. Symbols as in Table II.

Figure 9 shows the relation of the VE to the pulmonary arterial pressure (symbols as in Fig. 8). While in general they increase together, the correlation is poor and there are many cases who have a normal VE despite high pressure, including the three with the highest levels. The findings are somewhat similar when the pulmonary vascular resistance is considered instead of the pulmonary arterial pressure (Fig. 10). Although all the patients with the highest VE have high resistances, there are some with high resistance but normal VE.

Figure 11 shows the VE plotted against the indirect left atrial mean pressure. Here the relation appears to be closer, and though the range is wide we note that with a left atrial pressure of less than 20 mm. Hg only 1 out of 10 patients showed hyper-ventilation whereas when it was higher than 35 mm., 17 out of 21 patients did so. When the indirect left atrial pressure on exercise is studied in relation to the excess ventilation (the observed ventilation minus the anticipated ventilation expressed as a percentage of the latter, Fig. 12) the correlation is seen to be much closer and is highly significant ($p < 0.001$). Fig. 12 also includes our results from patients in Group II illustrated with triangles. It can be seen that their response in general falls within the range (heavy lines) obtained from the patients in Group III (mitral stenosis).

We have also observed 8 patients who were studied before and after mitral valvotomy, and the findings, which are shown in Table III, will be discussed later.

Group IV: Pulmonary Hypertension with normal left atrial pressure (9). The group is heterogeneous, consisting of two post-operative cases of mitral stenosis, two post-operative cases of ventricular septal defect and aorto-pulmonary window, respectively (the shunts having been abolished by surgery), one case of thromboembolic pulmonary hypertension, two cases of pulmonary hypertension secondary to lung disease, and two cases of idiopathic pulmonary hypertension. The common factor in all these patients is a resting pulmonary arterial systolic pressure above 50 mm. Hg in association with a normal left atrial pressure.

The importance of this group lies in the possibility of separating and evaluating pulmonary arterial pressure, pulmonary vascular resistance, and cardiac output as stimuli to ventilation.

Figure 13 shows the ventilation in relation to oxygen uptake on effort in this group. The cardiac output on exercise in all cases except one (open circle) lies below the lower limit of normal. Only two patients had a greater than normal ventilation on effort; one having thromboembolic and one

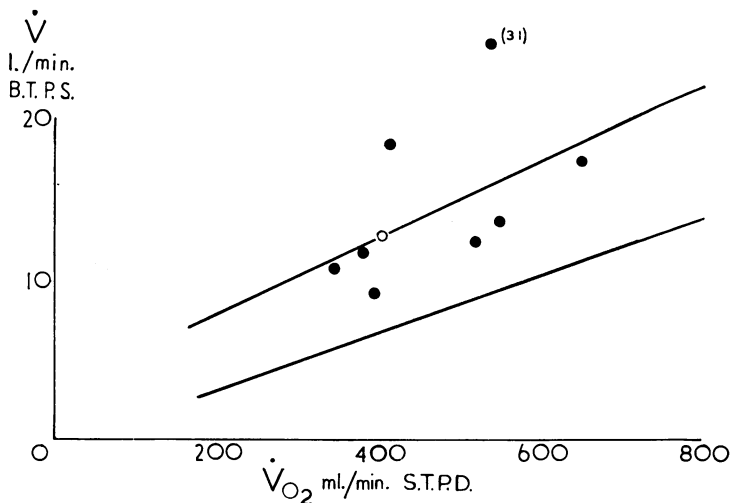


FIG. 13.—Ventilation and oxygen uptake in patients with pulmonary hypertension. The closed circles represent patients with a low cardiac output and the open circle represents one patient with a normal output on effort. The heavy lines represent limits of normal as in Fig. 1. It can be seen that the majority of these patients had a normal ventilatory response.

idiopathic pulmonary hypertension. Both had a reduced arterial oxygen saturation at rest and on effort, abnormalities that were also present in other patients without hyperventilation.

No relation was seen when the VE was plotted against the pulmonary arterial systolic pressure; or against the pulmonary vascular resistance.

Group V: Pulmonary Stenosis (27). The hæmodynamic findings (Table II) are similar to those

reported from this laboratory (Johnson, 1962) and elsewhere (Joos *et al.*, 1954; Lewis *et al.*, 1964).

In Fig. 14 we have plotted the cardiac output against the oxygen uptake in this group and it is seen to be below normal in a number of cases. In Fig. 15 the ventilation in relation to oxygen uptake is shown, the solid circles representing those patients with low cardiac output. There is no manifest difference in the ventilatory response to exercise between the low output cases and the others, and in

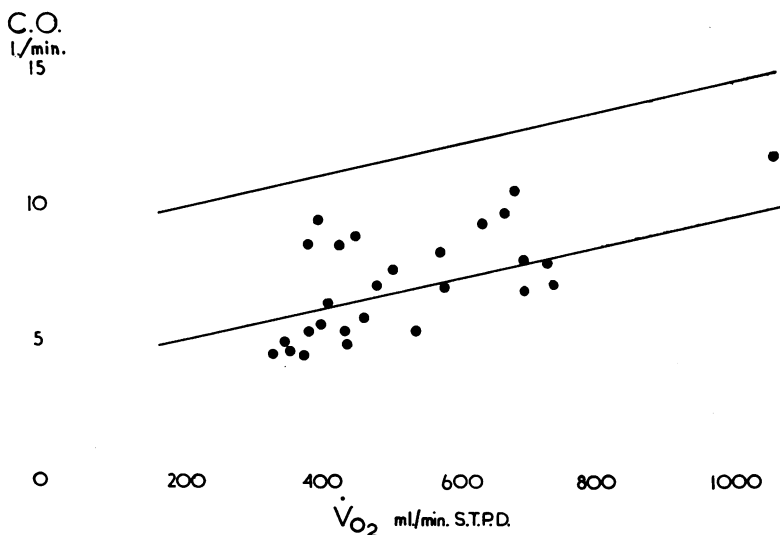


FIG. 14.—Cardiac output and oxygen uptake in patients with pulmonary stenosis. Heavy lines represent normal limits (see Fig. 3).

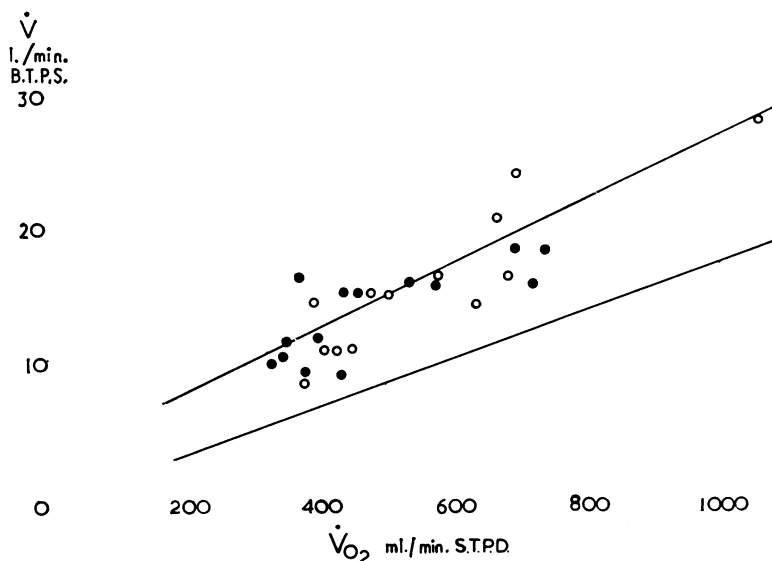


FIG. 15.—Ventilation and oxygen uptake in patients with pulmonary stenosis. Symbols as in Fig. 8. Heavy lines represent normal limits [see Fig. 1]. Most patients have a normal ventilatory response, and those patients with a low cardiac output on effort behave no differently than those with a reduced cardiac output.

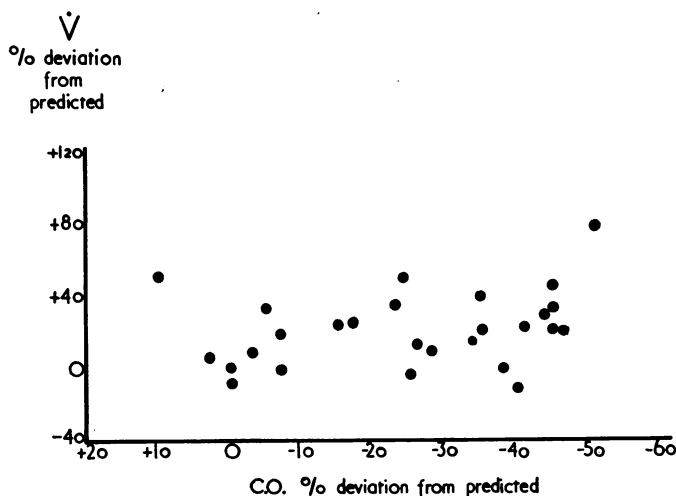


FIG. 16.—Percentage deviation of ventilation from predicted and percentage deviation of cardiac output from predicted (see text) in patients with pulmonary stenosis. There is no significant correlation between these variables ($r=0.3$, $0.1 < p < 0.2$).

about two-thirds of the patients the response is normal.

In order to examine more closely the relation between cardiac output and ventilation in this group, we have plotted the percentage deviation of each from normal in Fig. 16. So plotted, some

patients are seen to hyperventilate, but cardiac output is again not shown to be a determining factor since there is no significant relationship between these variables. Likewise, right ventricular systolic pressure and right atrial pressure do not appear to be related to the degree of ventilatory response.

DISCUSSION

Any attempt to discover what factor or factors are responsible for the hyperventilation so often associated with heart disease is made difficult by the frequency with which abnormalities in cardiac output, left atrial pressure, pulmonary arterial pressure and other physiological variables coexist. It is for this reason that we have selected different diagnostic groups in the hope that the factors which might be responsible for hyperventilation could be separated one from another, and their relative significance assessed.

The *cardiac output* is low in many forms of heart disease. The limitation of maximal oxygen uptake thus imposed on the body may be one of the factors associated with abnormal response to effort (McIlroy 1959). In the group of patients with pulmonary valve stenosis, the factors of pulmonary arterial and venous hypertension do not appear, and the function of the lungs is not usually disturbed. Here the effects of low cardiac output can therefore be seen in a purer form than in the other groups. Previous studies in such patients have yielded conflicting results: Sloman and Gandevia (1964) found a normal ventilatory response during upright exercise, while Lewis *et al.* (1964) found an exaggerated ventilatory response during supine exercise. Our results indicate that about one-third of the patients with pulmonary stenosis hyperventilate during both supine and upright (Gazetopoulos *et al.*, 1966) exercise. We have been unable to show any relationship in this condition between cardiac output and ventilation during mild supine exercise.

In patients with solitary pulmonary hypertension, a diminished cardiac output is commonly seen, and all our patients except one showed this abnormality. It is of interest that only two showed excessive ventilatory response. We have seen no relation between the lowering of the cardiac output and the ventilatory response on effort in this group of patients.

An impaired cardiac output is a frequent finding in mitral stenosis. Here again we have seen no relation between cardiac output and ventilatory response (Fig. 8). Only in the patients with aortic stenosis is there any suggestion that impairment of cardiac output might be linked to an excessive ventilatory response. Limitation of exercise output, however, is closely related to both indirect left atrial pressure (Fig. 5) and pulmonary arterial pressure (Fig. 6), which suggests that output alone may not be the determining factor. It thus appears that a lowered cardiac output is not in itself a significant cause of hyperventilation: a similar conclusion was reached by Donald *et al.* (1954),

Cotes (1955), Arnott (1963), and Sloman and Gandevia (1964).

The role of *pulmonary hypertension* will now be considered. A possible association between this variable and ventilation was suggested by the fact that hyperventilation, usually following an apnoeic interval, was seen to accompany a rise in pulmonary arterial pressure after experimental pulmonary embolism (Dunn, 1920; Halmagyi and Colebatch, 1961). Widdicombe (1963) noted, however, that a similar reaction could occur without an increase in pulmonary artery pressure (Horres and Bernthal, 1961), and De Bono and Gazetopoulos (1964) have shown in an experimental study in dogs that when 20 per cent saline is injected rapidly into the pulmonary artery, red cell agglutination, pulmonary hypertension, and hyperventilation quickly follow a period of apnoea. When hexadimethrine bromide (polybrene) is injected, a similar degree of pulmonary hypertension is observed without an accompanying ventilatory disturbance. These experimental studies suggest that under such circumstances pulmonary hypertension is not a direct stimulus to hyperventilation.

Our data on patients with solitary pulmonary hypertension are limited, but we have not been able to discern any association between the level of the pulmonary artery pressure and the ventilatory response. The fact that the ventilatory response was normal in the majority of our patients in this group is surprising in the face of the commonly held view that dyspnoea is a major symptom of primary pulmonary hypertension and that hyperventilation was the most striking finding even at rest (McIlroy, 1959). It is possible that the heterogeneity of the patients considered, and the fact that only two of them fitted into the picture of the progressive disease seen in young females and usually designated "primary pulmonary hypertension" may explain the discrepancy. We note, however, that McIlroy and Apthorp (1958) also found that hyperventilation was not uniformly associated with primary pulmonary hypertension.

In mitral valve disease a broad association is seen between pulmonary artery pressure and ventilatory equivalent, but it is noteworthy that some patients with the severest pulmonary hypertension had a normal ventilatory equivalent (Fig. 9). In the group with aortic stenosis or cardiomyopathy there is a broad correlation between ventilation and pulmonary artery pressure, but since the rise in the latter may be mediated via left atrial hypertension it obviously cannot be inculcated directly as an important factor in the genesis of hyperventilation. From this study, as discussed already, and other studies in patients with the Eisenmenger syndrome

and left-to-right shunts (Davies and Gazetopoulos, 1965), it appears, in keeping with early clinical observations (Brenner, 1935; East, 1940), that pulmonary hypertension *per se* is unlikely to be a factor of importance in determining the ventilatory response.

The place of *left atrial hypertension* can be discerned by reference only to the mitral and aortic groups. The importance of pulmonary venous congestion as a cause of hyperventilation and dyspnoea was suggested by Christie (1938) and Kountz, Smith, and Wright (1942). When the indirect left atrial pressure is plotted against the ventilatory equivalent in patients with mitral stenosis, as in Fig. 11, a broad relation is seen. When the left atrial pressure is considered relative to the excess ventilation (defined as the difference between observed ventilation and that anticipated for the work load), a relationship is quite apparent and is statistically highly significant ($p < 0.001$) (Fig. 12).

Studies in patients with mitral stenosis, before and after valvotomy, confirm that there is a much better correlation between clinical improvement and amelioration of the excessive ventilatory response on the one hand and a fall in pulmonary vascular pressures on the other, than there is with any rise in the cardiac output (Eliasch, 1952; Wade, Bishop, and Donald, 1954; Harvey *et al.*, 1955; Donald *et al.*, 1957). It is noted, however, that Donald and his associates, despite observing a good correlation between resting pulmonary wedge pressure and ventilation, found a very high exercise wedge pressure, sometimes of the order of 50 mm. Hg, with a normal ventilation in a number of patients after mitral valvotomy. These data can be interpreted as indicating a considerable degree of adaptation of the ventilatory control mechanism to a high left atrial pressure, and an important factor limiting hyperventilation could be its reduction following operation, even though it was still above normal. Pre-operative exercising wedge pressures were not measured in that study, but it may be that the fall in resting wedge pressure was paralleled by a fall in its exercise value.

We have observed 8 patients who were studied before and after valvotomy and the findings are shown in Table III. In Cases 1-6 operation was followed by a clear fall in the ventilation on effort together with a fall in pulmonary vascular pressures: the cardiac output remained unrelated to these. In Cases 7 and 8 significant hyperventilation remained; in Case 7 with unchanged wedge pressure; in Case 8 the hyperventilation is unexplained. The wedge pressures, though lower than before opera-

tion, remained high, though not as high as those reported by Donald *et al.* (1957); we note, however, that our exercise levels, as judged by the oxygen uptake, were not as high as theirs.

Despite the statistical correlation that exists between left atrial pressure and ventilation in patients with mitral stenosis as a group, there is clearly a wide individual difference between patients. For any given mean left atrial pressure the range of deviation of ventilatory response is large. It would be surprising, in view of the variability of individual response to all biological stimuli, if such a relationship were not seen, but the findings raise the very pertinent question as to the nature of this differing response between individuals. We have examined this from two standpoints: first whether or not a difference in any measured parameter exists, and secondly whether there is any evidence of adaptation to chronic increase in the left atrial pressure as already suggested from post-operative studies.

We have selected for this analysis patients with mitral stenosis, and divided them into two groups, those who hyperventilate and those who do not. In the first group all patients had an excessive ventilatory equivalent of 5.0 or more, and in the second group less than 3.5. In both groups, the exercise wedge pressure lay between 25 and 40 mm. Hg. We have thus excluded patients with exercise wedge pressures under 25 mm. Hg, because in our experience hyperventilation was rarely noted in this group. Similarly, with exercise wedge pressures over 40 mm. Hg hyperventilation was always present. We have observed no significant difference between these two groups in variables such as resting and exercise oxygen uptake, cardiac output, pulmonary artery systolic pressure, pulmonary vascular resistance, or exercise wedge pressure.

Again, in considering whether or not adaptation exists, it seems reasonable to suppose that if this were present the ratio of increase of wedge pressure with effort to the resting pressure would bear some relation to the increment of ventilation over the resting. Such a relation we have sought but failed to find.

The behaviour of the left atrial pressure-ventilation relationship in the aortic group is similar to that of the mitral (Fig. 12), and its close association with lowered cardiac output and with pulmonary hypertension has already been noted. It is of interest that there is such a close correlation between the impairment of anticipated cardiac output and the rise in indirect left atrial pressure on exercise. It appears in these patients that failure of the left ventricle manifests itself simultaneously by a fall

in output and a rise in left atrial pressure, for we have not seen any patients in whom a normal exercise output was maintained by means of a high left atrial pressure.

While there is therefore a statistical correlation between left atrial hypertension and hyperventilation, the nature of the individual variability in response remains unsolved. One major factor that may provide an important variable when attempting to compare one case with another, and which was not considered in this investigation, is *lung damage*. Though we have as yet little information about lung function under these circumstances, it is a subject for further studies.

We have also examined the pulmonary vascular resistance, the presence or absence of atrial fibrillation, the level of ventricular cavity pressures, the systemic arterial pressures, the right atrial pressure, and the blood haemoglobin, and have found none of these to bear any relation to the level of ventilation.

In an attempt to clarify some of the issues raised, we intend to discuss in a subsequent paper the changes in blood gases that occur with exercise, and to examine whether or not these play any part in the determination of the ventilatory response.

SUMMARY

The relation between haemodynamic changes and ventilation during cardiac catheterization has been studied in several groups of patients with heart disease at rest and on exercise. A good correlation between pulmonary venous hypertension and ventilation had been confirmed in those cases where the former was present, such as in mitral and aortic valve disease. Neither pulmonary hypertension *per se* nor a lowered cardiac output could be implicated in the genesis of effort hyperventilation during mild supine exercise on the catheter table.

This work has been supported by grants from Guy's Hospital Endowments Fund and from Boehringer Ingelheim Ltd., to whom we are accordingly indebted. We would also like to thank our many colleagues—physicians, technicians, nurses, and secretaries—who have helped us with this study.

REFERENCES

- Arnott, M. W. (1963). The lungs in mitral stenosis. *Brit. med. J.*, **2**, 765.
- Astrand, P. O. (1952). *Experimental Studies of Physical Working Capacity in Relation to Sex and Age*. Munksgaard, Copenhagen.
- Aviado, D. M., and Schmidt, C. F. (1955). Reflexes from stretch receptors in blood vessels, heart and lungs. *Physiol. Rev.*, **35**, 247.
- Barratt-Boyes, B. G., and Wood, E. H. (1957). Hemodynamic response of healthy subjects to exercise in the supine position while breathing oxygen. *J. appl. Physiol.*, **11**, 129.
- Blount, S. G., McCord, M. C., and Anderson, L. L. (1952). The alveolar-arterial oxygen pressure gradient in mitral stenosis. *J. clin. Invest.*, **31**, 840.
- Brenner, O. (1935). Pathology of the vessels of the pulmonary circulation. Part IV. *Arch. intern. Med.*, **56**, 976.
- Carroll, D., Cohn, J. E., and Riley, R. L. (1953). Pulmonary function in mitral valvular disease: distribution and diffusion characteristics in resting patients. *J. clin. Invest.*, **32**, 510.
- Christie, R. V. (1938). Dyspnoea: a review. *Quart. J. Med.*, **31** (n.s. 7), 421.
- Costantin, L. L. (1959). Effect of pulmonary congestion on vagal afferent activity. *Amer. J. Physiol.*, **196**, 49.
- Cotes, J. E. (1955). The role of oxygen, carbon dioxide and lactic acid in the ventilatory response to exercise in patients with mitral stenosis. *Clin. Sci.*, **14**, 317.
- Cunningham, D. J. C. (1963). Some quantitative aspects of the regulation of human respiration in exercise. *Brit. med. Bull.*, **19**, 25.
- Dawes, G. S., and Comroe, J. H. (1954). Chemoreflexes from the heart and lungs. *Physiol. Rev.*, **34**, 167.
- Davies, H., and Gazetopoulos, N. (1965). Haemodynamic ventilatory and metabolic changes on exercise in patients with left-to-right shunts. To be published.
- , —, and Oliver, C. (1965). Ventilatory and metabolic response to effort in normal subjects. *Clin. Sci.* In the press.
- De Bono, A., and Gazetopoulos, N. (1964). Experimental pulmonary embolism due to red cell aggregation. *Thorax*, **19**, 244.
- Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R., and Sawyer, C. G. (1951). Effect of exercise on circulatory dynamics of normal individuals. *J. appl. Physiol.*, **3**, 439.
- Donald, K. W. (1959). Disturbances in pulmonary function in mitral stenosis and left heart failure. *Progr. cardiovascular Dis.*, **1**, 298.
- , Bishop, J. M., Cumming, G., and Wade, O. L. (1955). The effect of exercise on the cardiac output and circulatory dynamics of normal subjects. *Clin. Sci.*, **14**, 37.
- , —, and Wade, O. L. (1954). A study of minute to minute changes of arterio-venous oxygen content difference, oxygen uptake and cardiac output and rate of achievement of a steady state during exercise in rheumatic heart disease. *J. clin. Invest.*, **33**, 1146.
- , —, and Wormald, P. N. (1957). Cardiac respiratory function two years after mitral valvotomy. *Clin. Sci.*, **16**, 325.
- , and Christie, R. V. (1949). A new method of clinical spirometry. *Clin. Sci.*, **8**, 21.
- , Gloster, J., Harris, E. A., Reeves, J., and Harris, P. (1961). The production of lactic acid during exercise in normal subjects and in patients with rheumatic heart disease. *Amer. Heart J.*, **62**, 494.
- Downing, S. E. (1957). Reflex effects of acute hypertension in the pulmonary vascular bed of the dog. *Yale J. Biol. Med.*, **30**, 43.
- Dunn, J. S. (1920). The effects of multiple embolism on pulmonary arterioles. *Quart. J. Med.*, **13**, 129.
- East, T. (1940). Pulmonary hypertension. *Brit. Heart J.*, **2**, 189.
- Eliasch, H. (1952). The pulmonary circulation at rest and on effort in mitral stenosis. *Scand. J. clin. Lab. Invest.*, **4**, Suppl. 4.
- Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Courmand, A., and Richards, D. W., Jr. (1952). Hemodynamic studies in rheumatic heart disease. *Circulation*, **6**, 688.

- Frank, N. R., Cugell, D. W., Gaensler, E. A., and Ellis, L. B. (1953). Ventilatory studies in mitral stenosis. A comparison with findings in primary pulmonary disease. *Amer. J. Med.*, **15**, 60.
- Freedman, M. E., Snider, G. L., Brostoff, P., Kimelblot, S., and Katz, L. N. (1955). Effects of training on response of cardiac output to muscular exercise in athletes. *J. appl. Physiol.*, **8**, 37.
- Gazetopoulos, N., Davies, H., and Deuchar, D. (1966). Ventilation in relation to arterial and venous blood chemistry in heart disease. *Brit. Heart J.*, **28**, 16.
- Gorlin, R., Sawyer, C. G., Haynes, F. W., Goodale, W. T., and Dexter, L. (1951). Effects of exercise on circulatory dynamics in mitral stenosis. *Amer. Heart J.*, **41**, 192.
- Gray, J. S. (1950). *Pulmonary Ventilation and its Physiological Regulation*. Thomas, Springfield, Illinois.
- Grodins, F. S. (1950). Analysis of factors concerned in regulation of breathing in exercise. *Physiol. Rev.*, **30**, 220.
- Halmagyi, D. F. J., and Colebatch, H. J. H. (1961). Cardio-respiratory effects of experimental lung embolism. *J. clin. Invest.*, **40**, 1785.
- Harris, P., Bateman, M., and Gloster, J. (1962). Relations between the cardio-respiratory effects of exercise and the arterial concentration of lactate and pyruvate in patients with rheumatic heart disease. *Clin. Sci.*, **23**, 531.
- Harrison, T. R., and Pilcher, C. (1930). Studies in congestive heart failure. II. The respiratory exchange during and after exercise. *J. clin. Invest.*, **8**, 291.
- Harvey, R. M., Ferrer, M. I., Samet, P., Bader, R. A., Bader, M. E., Cournand, A., and Richards, D. W. (1955). Mechanical and myocardial factors in rheumatic heart disease with mitral stenosis. *Circulation*, **11**, 531.
- Hickam, J. B., and Cargill, W. H. (1948). Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J. clin. Invest.*, **27**, 10.
- Horres, A. D., and Bernthal, T. (1961). Localized multiple minute pulmonary embolism and breathing. *J. appl. Physiol.*, **16**, 842.
- Huckabee, W. E., and Judson, W. E. (1958). The role of anaerobic metabolism in the performance of mild muscular work. I. Relationship to oxygen consumption and cardiac output, and the effect of congestive heart failure. *J. clin. Invest.*, **37**, 1577.
- Johnson, A. M. (1962). Impaired exercise response and other residua of pulmonary stenosis after valvotomy. *Brit. Heart J.*, **24**, 375.
- Joos, H. A., Yu, P. N., Lovejoy, F. W., Nye, R. E., Jr., and Simpson, J. H. (1954). Clinical and hemodynamic studies in congenital pulmonic stenosis with intact ventricular septum. *Amer. J. Med.*, **17**, 6.
- Katz, L. N., Soskin, S., Schutz, W. J., Ackerman, W., and Plaut, J. L. (1934). A "metabolic exercise tolerance test" for patients with cardiac disease. *Arch. intern. Med.*, **53**, 710.
- Korn, D., Bensch, K., Liebow, A. A., and Castleman, B. (1960). Multiple minute pulmonary tumors resembling chemodectomas. *Amer. J. Path.*, **37**, 641.
- Kountz, W. B., Smith, J. R., and Wright, S. T. (1942). Observations on the effect of tourniquets on acute cardiac crises, normal subjects, and chronic heart failure. *Amer. Heart J.*, **23**, 624.
- Krahl, V. E. (1960). The glomus pulmonale. A preliminary report. *Bull. Sch. Med. Maryland*, **45**, 36.
- Lewis, C. S., Samuels, A. J., Daines, M. C., and Hecht, H. H. (1952). Chronic lung disease, polycythemia and congestive heart failure. Cardiorespiratory, vascular and renal adjustments in cor pulmonale. *Circulation*, **6**, 874.
- Lewis, J. M., Montero, A. C., Kinard, S. A., Dennis, E. W., and Alexander, J. K. (1964). Hemodynamic response to exercise in isolated pulmonic stenosis. *Circulation*, **29**, 854.
- McIlroy, M. B. (1959). Dyspnoea and the work of breathing in diseases of the heart and lungs. *Progr. cardiovasc. Dis.*, **1**, 284.
- , and Apthorp, G. H. (1958). Pulmonary function in pulmonary hypertension. *Brit. Heart J.*, **20**, 397.
- Meakins, J., and Long, C. N. H. (1927). Oxygen consumption, oxygen debt and lactic acid in circulatory failure. *J. clin. Invest.*, **4**, 273.
- Nonidez, J. F. (1936). Observations on the blood supply and the innervation of the aortic paraganglion of the cat. *J. Anat. (Lond.)*, **70**, 215.
- Raine, J., and Bishop, J. M. (1963). The distribution of alveolar ventilation in mitral stenosis at rest and after exercise. *Clin. Sci.*, **24**, 63.
- Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournand, A. (1948). Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. *Amer. J. Physiol.*, **152**, 373.
- , Johns, C. J., Cohen, G., Cohn, J. E., Carroll, D. G., and Shepard, R. H. (1956). The diffusing capacity of the lungs in patients with mitral stenosis studied post-operatively. *J. clin. Invest.*, **35**, 1008.
- Sloman, G., and Gandevia, B. (1964). Ventilatory capacity and exercise ventilation in congenital and acquired cardiac disease. *Brit. Heart J.*, **26**, 121.
- Slonim, N. B., Ravin, A., Balchum, O. J., and Dressler, S. H. (1954). The effect of mild exercise in the supine position on the pulmonary arterial pressure of five normal human subjects. *J. clin. Invest.*, **33**, 1022.
- Wade, O. L., Bishop, J. M., and Donald, K. W. (1954). The effect of mitral valvotomy on cardio-respiratory function. *Clin. Sci.*, **13**, 511.
- Wahlund, H. (1948). Determination of the physical working capacity. A physiological and clinical study with special reference to standardization of cardio-pulmonary functional tests. *Acta med. scand.*, Suppl. 215.
- West, J. R., Bliss, H. A., Wood, J. A., and Richards, D. W. (1953). Pulmonary function in rheumatic heart disease and its relation to exertional dyspnoea in ambulatory patients. *Circulation*, **8**, 178.
- Widdicombe, J. G. (1954). The site of pulmonary stretch receptors in the cat. *J. Physiol. (Lond.)*, **125**, 336.
- (1961). Respiratory reflexes in man and other mammalian species. *Clin. Sci.*, **21**, 163.
- (1963). Respiratory reflexes from the lungs. *Brit. med. Bull.*, **19**, 15.
- Wood, P. (1954). An appreciation of mitral stenosis. Part I. Clinical features. *Brit. med. J.*, **1**, 1051.